PU.1 and C/EBP(alpha) synergistically program distinct response to NF-kappaB activation through establishing monocyte specific enhancers.

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Public Summary:
A lot of human genes are only expressed in certain tissues, and such tissue-specific pattern is controlled by certain small DNA-sequences called enhancers. It has been discovered that in human genome, enhancers are associated with certain proteins and/or RNA product. These knowledge has allowed the identification of enhancers in a genome scale with the help of modern genomic technologies. On the other hand, although tissue-specific gene expression has been found to be highly correlated with tissue specific enhancer activity, the molecular mechanisms of such correlation have not been fully characterized. Based on recent literature and our own work, this point-of-view article proposes a model in which enhancers function as a central platform integrating all the inputs, including information from both within the cell and outside the cells, and producing highly specific gene expression programs.

Scientific Abstract:
Unraveling the complexity of transcriptional programs coded by different cell types has been one of the central goals of cell biology. By using genome-wide location analysis, we examined how two different cell types generate different responses to the NF-kappaB signaling pathway. We showed that, after TNF-alpha treatment, the NF-kappaB p65 subunit binds to distinct genome locations and subsequently induces different subsets of genes in human monocytic THP-1 cells versus HeLa cells. Interestingly, the differential p65 binding in two cell types correlates with preexisting cell type-specific enhancers before TNF-alpha stimulation, marked by histone modifications. We also found that two transcription factors, PU.1 and C/EBPalpha, appear to synergistically mediate enhancer creation and affect NF-kappaB target selection in THP-1 cells. In HeLa cells, coexpression of PU.1 and C/EBPalpha conferred TNF-alpha responsiveness to a subset of THP-1-specific NF-kappaB target genes. These results suggest that the diversity of transcriptional programs in mammalian cells arises, at least in part, from preexisting enhancers that are established by cell-specific transcription factors.

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